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A Next-Generation TRK Kinase Inhibitor Overcomes Acquired Resistance to Prior TRK Kinase Inhibition in Patients with TRK Fusion–Positive Solid Tumors ... 963

**Précis:** Parallel development of the first-generation TRK TKI larotrectinib with the next-generation TKI LOXO-195 allowed for rapid use of LOXO-195 to treat patients with acquired larotrectinib resistance.
See commentary, p. 934

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**Spotlight on Ibrutinib in PCNSL: Adding Another Feather to Its Cap** ........ 940
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Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma


Précis: In patients with high-grade ovarian carcinoma treated with the PARP inhibitor rucaparib, secondary reversion mutations in HR genes restore the open reading frame and HR activity to confer resistance. See commentary, p. 937
See article, p. 999
See article, p. 1006

Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors


Précis: Multiclonal BRCA2 reversion mutations were detected in circulating cell-free DNA from two patients with metastatic prostate cancer after PARP inhibitor treatment, suggesting a mechanism of resistance. See commentary, p. 937
See article, p. 984
See article, p. 1006

Circulating Cell-Free DNA to Guide Prostate Cancer Treatment with PARP Inhibition


Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma


Discovery and Optimization of HKT288, a Cadherin-6-Targeting ADC for the Treatment of Ovarian and Renal Cancers


Précis: Sequencing cfDNA from patients with olaparib-treated prostate cancer reveals that reduced cfDNA is a biomarker of response and can harbor resistance mutations that may guide treatment. See commentary, p. 940
See article, p. 999
See article, p. 1018
PARP inhibitors (PARPi) have demonstrated activity in patients with mutations in homologous recombination (HR) genes such as BRCA1 and BRCA2. Three related studies identified HR gene reversion mutations that confer resistance to PARPi. Kondrashova and colleagues discovered secondary reversion mutations in BRCA1, RAD51C, and RAD51D in patients with PARPi-resistant ovarian cancer. Similarly, Quigley, Alumkal, and colleagues identified BRCA2 reversion mutations associated with PARPi resistance in circulating cell-free DNA (cfDNA) from two patients with prostate cancer. Finally, Goodall, Mateo, and colleagues found secondary reversion mutations in BRCA2 and PALB2 in cfDNA from patients with PARPi-resistant metastatic prostate cancer. Together, these studies demonstrate that HR gene reversion mutations can promote resistance to PARPi. For details, please see the article by Kondrashova and colleagues on page 984, the article by Quigley, Alumkal, and colleagues on page 999, and the article by Goodall, Mateo, and colleagues on page 1006.